Attorney's Docket No.: 06275-150003 / D 1841-3P US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Carl-Axel Bauer *et al.*
Serial No. : 10/010,283
Filed : November 13, 2001
Title : NEW USE FOR BUDESONIDE AND FORMOTEROL

Art Unit : 1617
Examiner : Jennifer M. Kim

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF JAN TROFAST UNDER 37 CFR §1.114(c)

I, Jan Trofast, declare as follows:

1. I have been a scientist at AstraZeneca R&D (formerly Astra AB) since 1979 in the division of Medicinal chemistry and Pharmaceutical & Analytical R&D at AstraZeneca. I received a Ph.D. in organic chemistry in 1978 from Lund Institute of Technology, Lund, Sweden. I have been studying and conducting research in the field of respiratory disorders since 1979, and I am an expert in this field. I am a co-inventor of the invention claimed in this application.

2. The invention claimed in this application features a method of treating chronic obstructive pulmonary disease (COPD) by administering to a patient, via inhalation, (i) formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; and (ii) budesonide, the molar ratio of (i) to (ii) being from 1:2500 to 12:1.

3. I have read the Examiner's Answer to the Appeal Brief mailed December 29, 2003.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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4. I am an inventor named in the prior art reference, Carling *et al.* (WO 93/11773).

5. The subject of Carling *et al.* is the treatment of asthma with a β2 agonist (formoterol) and a steroid (budesonide) to treat a respiratory disorder such as asthma. Carling *et al.* states at page 4, lines 19-28 that the "invention relates to improvements in the treatment of mild as well as severe asthma and *other respiratory disorders*." The Examiner asserts, in the Examiner's Answer, that this mention of other respiratory disorders would have been understood by the artisan to include COPD. I cannot agree with this interpretation.

The phrase "respiratory disorders" has in fact been used in the medical literature to refer to a wide and varying range of disorders, the only common thread being an effect on the respiratory function of the patient. The lengthy list of such disorders, includes, for example, not only asthma and COPD, but also respiratory infections such as tuberculosis and bronchopulmonary aspergillosis, cough, asbestos-related disease and other diseases resulting from the inhalation of particulate matter, different forms of lung cancer, acute respiratory distress syndrome, toxic lung injury, cystic fibrosis, interstitial lung diseases (such as idiopathic pulmonary fibrosis and the like), alveolitis, and sarcoidosis (see, for example, "Respiratory Medicine," vol. 1, 3rd edition, Gibson *et al.*, *eds.*, Table of Contents, submitted herewith).

In the context of Carling *et al.*, the phrase "other respiratory disorders" was not meant to be interpreted so broadly, nor would someone in my field reading Carling *et al.* in 1998[1] have been likely to interpret it in this manner. Instead, the term "other respiratory disorders," as used by Carling *et al.*, was intended to and would have been understood to refer to respiratory disorders similar to asthma i.e. mainly of bronchospastic nature.

6. There exist a number of respiratory disorders that are similar to asthma in both their pathophysiological features and their treatment protocol, for example extrinsic atopic

[1] (The invention claimed in the present application is entitled to a priority date of November 23, 1998.).

asthma, extrinsic non-atopic asthma, intrinsic asthma, wheezing in children and bronchospastic cough. In some cases, these disorders are referred to collectively as "asthma." However, because they are different conditions they may also be referred to as "asthma and other respiratory disorders," as my co-inventors and I did in the Carling *et al.* reference. Buist ("Definitions," in Asthma and COPD, Barnes *et al.*, eds. London: Academic Press, 2002, pages 3-6) reports at page 3, column 1, the definition of asthma from the Expert Panel 2 Report (the current U.S. asthma guideline) as:

> a chronic inflammatory disorder of the airways...In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough...These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment...[emphasis added].

Thus a key pathophysiological feature common to these disorders is reversible airflow obstruction, which is monitored by spirometry or measurements of peak expiratory flow rate. These disorders are treated in similar fashion. They differ significantly, both in their pathophysiological features and their modes of treatment, from the wide range of non-asthma-like respiratory disorders listed above and in the medical literature. Thus, for example, these disorders differ significantly in both their pathology and their treatment from unrelated respiratory disorders such as lung cancer or asbestosis.

7. A diagnosis of asthma requires the exclusion of other causes of similar symptoms. COPD is the most common differential diagnosis in adults. The clinical features and pathophysiology of COPD and asthma indicate that there is some overlap between the conditions. For example, chronic inflammation underlies both diseases, but the nature of the inflammation differs. Both COPD and asthma have a reversible airflow obstruction component, but airflow obstruction in COPD is not fully reversible. In fact COPD is characterized by a progressive development of airflow limitation. Buist (2002) reports the definition of COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines: "A disease state characterized by progressive development of airflow limitation that is not fully reversible..." (Buist, page 3, column 1).

Sufferers of COPD and asthma also respond differently to specific therapies. For example, as discussed in Barnes *et al.* (*Eur. Resp. Jour.* 22:672-688, 2003) at page 672, column 2, and page 673, column 1:

> COPD is characterized by acceleration in the normal decline of lung function seen with age. The slowly progressive airflow limitation leads to disability and premature death and is quite different from the variable airway obstruction and symptoms in asthma, which rarely progress in severity. While COPD and asthma both involve inflammation in the respiratory tract there are marked differences in the nature of the inflammatory process, with differences in inflammatory cells, mediators, response to inflammation, anatomical distribution and response to anti-inflammatory therapy [emphasis added].

Buist further reports at page 4, column 1:

> Perhaps the single most important difference between the two diseases is the nature of the inflammation: it is primarily eosinophilic, CD4-driven in asthma and neutrophilic, CD8-driven in COPD...There is ample evidence now that inhaled corticosteroids are effective against the eosinophilic inflammation that is characteristic of asthma...but largely ineffective against the primarily neutrophilic inflammation seen in COPD...

There is generally a lack of efficient medication for COPD, and therefore the British Thoracic Society prepared guidelines specifically for the management of COPD. These guidelines do not include recommendations for treatment of asthma.

This evidence, considered collectively, indicates that COPD would not be considered to be a respiratory disorder similar to asthma by those of skill in the art.

8. Minor symptoms of COPD, for example bronchial constriction, are reversible and generally treatable by a bronchodilator such as a β2 agonist, an anticholinergic, or a theophylline. These minor reversible symptoms are similar to asthmatic symptoms. The major symptoms of COPD, however, include exacerbations that were not treatable by the classes of drugs that existed at the time of filing of Carling *et al.* (December 1991). The level

of skill in the art of treating COPD and asthma in 1991, at the time Carling *et al.* was written, was such that an expert in the field would have predicted that treatment of COPD with a β2-agonist and corticosteroid combination would be unsuccessful, particularly for the relief of exacerbations that lead to progressive airflow obstruction. As a result, at the time of the Carling *et al.* reference my co-inventors and I did not contemplate using our β2 agonist/corticosteroid combination to treat COPD.

Calverley *et al.* (*Eur. Resp. J.* 22:912-919, 2003) report the successful prevention of exacerbations in COPD patients using a combination of inhaled corticosteroid (budesonide) and β2 agonist (formoterol). Table 3 of Calverley *et al.* shows that the combination of budesonide and formoterol reduces the number of exacerbations more effectively than either budesonide or formoterol alone. Table 3 shows that the number of exacerbations per year (mean rate per patient per year) was 1.80 during treatment with placebo and a near-equivalent 1.85 during treatment with the β2 agonist formoterol. Exacerbations were mildly reduced following treatment with the corticosteroid budesonide (1.60 mean rate per patient per year) although this decrease was still not significant as compared to treatment with placebo. Treatment with the combination of budesonide and formoterol reduced the rate of exacerbations to 1.38, a significant reduction as compared to treatment with placebo. This result was surprising given the low efficacy or ineffectiveness of treatment with either budesonide or formoterol alone. The authors offer a biological explanation for this result, saying "[i]t...seems that formoterol and budesonide in combination are more effective at reducing proliferation of airway smooth muscle than either drug alone, as a result of synchronised cellular signalling..." (page 918, column 2).

Rabe *et al.* (*Eur. Respir. J.*, 22:874-875, 2003) responds to the Calverley study in an editorial published in the same journal issue as Calverley *et al.*:

> We have all witnessed the heated discussions around inhaled steroids in COPD and have seen and read the data that confirm that asthma and COPD are completely different diseases, clinically and biologically. I can see the role of long-acting bronchodilators for the treatment of COPD, an issue that is already addressed in the updated Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines... but the use of inhaled steroids and combination therapy as in asthma? Is this a "one size fits all"

> strategy that is driven by commercial interests? And were we all wrong, does this mean we no longer need to differentiate between asthma and COPD...? [Rabe, page 874, column 1].

Thus, asthma and COPD are still, as they were at the time of the Carling *et al.* reference and at the time of the present invention, and even in light of the Calverley study, considered by those of skill in the art to be very different diseases that require very different treatment protocols. They cannot properly be linked or considered as similar disorders, as they have as little in common as most of the other "respiratory disorders" listed in paragraph 5 above.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Date: 24 Feb. 2004

Jan Trofast